



Management of young women with early breast cancer

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ABSTRACT

Breast cancer is still the most frequent cancer diagnosed in women aged ≤40 years and the primary cause of death in this age group. The management of these patients needs a dedicated approach involving a multidisciplinary team that takes into account their treatment and survivorship issues. The present review aims to provide a perspective on the many challenges associated with treatment of young women with early breast cancer. We will focus on the standard (neo)adjuvant treatment, highlighting the paucity of age-specific results about the available genomic signatures, the groundbreaking landscape of adjuvant endocrine therapy and the relevant issue of the fertility preservation.

INTRODUCTION

Breast cancer in young women (defined as breast cancer in women aged ≤40 years) represents less than 7% of all diagnosed breast cancer in developed countries.¹ In low-income countries, the proportion of cases of breast cancer diagnosed among young women is higher (up to 20%). These differences may be due to environmental factors, genetic differences or reproductive behaviour between different regions.^{2,3}

Even if it can be considered a rare disease, breast cancer is the most commonly diagnosed malignancy among adult women and the primary cause of death in this age group.⁴ Breast cancer arising in young women is characterised by a more aggressive behaviour, greater proportion of high-grade, triple-negative and HER2-positive disease, the more advanced stage at diagnosis as compared with the older counterpart.⁵

The prognostic value of young age varies by breast cancer subtypes: young age does not seem to be a predictor of worse outcome in patients with triple-negative and HER2-positive subtypes, while it has a substantial prognostic role in luminal tumours.⁶ This divergence may reflect differences in tumour biology, inappropriate treatment (ie, the absence of ovarian suppression as part of the endocrine treatment) and lower therapeutic

adherence and persistence to endocrine therapies.⁶

ADJUVANT SYSTEMIC TREATMENT

International guidelines for the management of breast cancer in young women state that adjuvant systemic treatment decisions in this setting should be similar to those in older patients. Specifically, treatment decision-making should be mainly driven by the biological characteristics of the tumour (including tumour size, nodal involvement, grade, proliferation, hormonal receptor status and HER-2 expression), patient's preferences and comorbidities; importantly, young age itself should not be considered a reason to use more aggressive treatments.⁷

(NEO)ADJUVANT CHEMOTHERAPY

The optimal adjuvant chemotherapy regimen specifically for young women is not currently defined. Yet, the standard regimen is the combination of an anthracycline, alkylating agent and taxane similar to that in older patient candidates to adjuvant chemotherapy for early breast cancer.⁷

Dose-dense chemotherapy is a mainstay adjuvant treatment for high-risk patients breast cancer.⁸ To specifically investigate the role of the dose-dense schedule in young patients with breast cancer, a pooled analysis restricted to premenopausal women enrolled in two adjuvant chemotherapy trials has been recently performed.⁹ In high-risk premenopausal patients with breast cancer, the use of a dose-dense regimen was associated with better overall survival (HR 0.71, 95% CI 0.54 to 0.95, $p=0.021$), as compared with standard duration regimen, without further risk of chemotherapy-induced amenorrhoea.⁹ Also the preliminary results of the meta-analysis based on individual patient data conducted by the Early Breast Cancer Trialists Collaborative Group confirmed that increasing the dose density of adjuvant chemotherapy led to

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significant improvement in breast cancer recurrence and mortality, regardless of patients' age.¹⁰

In the light of the above results, dose-dense anthracycline and taxane-based regimen should be regarded as the preferred option in high-risk premenopausal patients with breast cancer who are candidates to receive chemotherapy. Another potential added benefit of a shorter chemotherapy duration in young patients may be the quicker recovery from the negative side effects of the treatment (such as the alopecia) with positive impact also on their return to their job.⁹

The role of neoadjuvant platinum-based chemotherapy in patients with triple-negative breast cancer is still controversial. A recent meta-analysis showed that platinum-based neoadjuvant chemotherapy significantly increased rates of pathological complete response rate from 37.0% to 52.1% ($p < 0.001$), at the cost of higher toxicity.¹¹ Being the triple-negative phenotype more frequent in young patients, the addition of a platinum agent to a standard neoadjuvant chemotherapy may be considered an appropriate approach particularly in this group of women.

Recently, multigene prognostic tests have been developed to assist clinicians in the process of adjuvant decision, in addition to traditional clinical pathological features.⁷ The 21-gene recurrence score assay (Oncotype DX) is one of the available gene expression signatures able to provide prognostic information that can help in identifying the patients with hormone receptor-positive breast cancer who may benefit from the addition of chemotherapy. In the TailorX study, the use of chemotherapy in the younger women with an intermediate recurrence score of 16–25 (46% of patients in this age group) was associated with improved survival.¹² However, only 13% of these women received ovarian function suppression that is currently considered a key part of endocrine therapy in premenopausal patients at higher risk of disease recurrence. Further research on this topic is required to better clarify the potential role of genomic signatures to add prognostic information in young patients to help discussing the additional benefit of chemotherapy in this setting.

ADJUVANT ENDOCRINE THERAPY

The choice of the most appropriate adjuvant endocrine treatment is of particular importance among premenopausal women considering the negative prognostic value of young age in this tumour subtype and the many options that are now available.

Recently, the panorama of adjuvant endocrine therapy for premenopausal patients has dramatically changed and the choice of the best approach has become quite complex.¹³

The updated results of the Tamoxifen and Exemestane trial (TEXT) and Suppression of Ovarian Function Trial (SOFT) have enriched the landscape of adjuvant endocrine therapy for premenopausal patients with breast cancer.¹⁴

The SOFT trial randomly assigned 3066 premenopausal women to receive 5 years of tamoxifen alone, ovarian function suppression combined with tamoxifen or exemestane. After a median follow-up of 8 years, the addition of ovarian function suppression (OFS) to tamoxifen significantly improved disease-free survival (HR 0.76, 95% CI 0.60 to 0.97), which translated into an absolute difference of 4.2 percentage points. The absolute benefits were larger in the group of patients who remained premenopausal after previous chemotherapy, with higher risk clinical pathological features and higher risk of relapse.¹⁴

In the joint analysis of the SOFT and TEXT, 4690 premenopausal patients were randomised to receive OFS combined with tamoxifen or exemestane. At a median follow-up of 9 years, the treatment with exemestane plus OFS was associated to higher rates of disease-free survival (86.8% vs 82.8%, 4.0% absolute benefit) and freedom from distant recurrence (91.8% vs 89.7%, 2.1% absolute benefit), compared with tamoxifen plus ovarian function suppression. Based on the available evidence on this regard, oestrogen receptor-positive/HER2-negative premenopausal patients with early breast cancer considered at high risk of relapse, and treated with adjuvant chemotherapy, derived greater benefit to the combination of exemestane plus OFS, being the suitable candidates for this treatment strategy.¹⁴ On the other hand, tamoxifen alone or associated with OFS is an option for young women with less aggressive characteristics, and for those who cannot tolerate the side effects of aromatase inhibitors.

Up to 20% of the young patients stopped therapies prematurely, especially those younger than 35 years, due to the related adverse events.¹⁵ Since early discontinuation of endocrine therapy is associated with worse prognosis, patients should be aware of the toxicities of the different therapies and appropriate supportive measures are needed to increase the compliance to long-term endocrine therapy.¹⁶

The substudy SOFT-Estrogen Substudy (EST) showed that up to 20% of women treated with exemestane plus OFS did not experience a complete ovarian suppression.¹⁷ Therefore, in young patients on exemestane a monitoring of oestradiol levels and the possible onset of premenopausal symptoms is recommended (ie, vaginal bleeding): in case of inadequate ovarian suppression, patients should be shifted to tamoxifen in addition to OFS.

The best timing of beginning pharmacological OFS in case of adjuvant chemotherapy is not still clearly defined, although a concomitant administration has the additional capability to preserve ovarian function without negative impact on the long-term outcome.^{18 19}

To date, no data are available on extended therapy beyond 5 years for patients who underwent exemestane combined with OFS.

PRESERVATION OF FERTILITY

Many young women have not completed the family planning at the time of breast cancer diagnosis.^{20 21} Taking also into account the improved survival, oncologists must now consider also the long-term side effects associated with the use of the proposed anticancer treatments. International guidelines recommend that all young patients should be properly and promptly counselled about the impact of anticancer treatment on their fertility and the available techniques for fertility preservation.^{7 22} Failure to address these vulnerable topics can negatively influence the compliance to the proposed anticancer therapies, potentially negatively affecting prognosis.²⁰

Nowadays, different techniques for fertility preservation in these patients are available: embryo and oocyte cryopreservation are the main options to be proposed.²³ The role of temporary ovarian suppression with gonadotropin-releasing hormone agonists (GnRHa) during chemotherapy has been recently evaluated in a meta-analysis of individual data as a strategy for ovarian function and fertility preservation.¹⁹ Concomitant administration of GnRHa and chemotherapy was associated with a significant reduced risk of developing iatrogenic premature ovarian insufficiency (adjusted OR 0.38; 95% CI 0.26 to 0.57) and significantly higher chances of having a post-treatment pregnancy (incidence rate ratio 1.83; 95% CI 1.06 to 3.15). No detrimental impact on long-term outcomes was observed.¹⁹ Therefore, GnRHa during chemotherapy can now be offered to premenopausal patient candidates to receive chemotherapy and interested in preserving ovarian function and potential fertility.^{7 23}

The issue of the fertility preservation is becoming more relevant also for the recent findings that pregnancy after breast cancer did not affect prognosis and should not be discouraged including among women with hormone receptor-positive disease.²⁴

CONCLUSIONS

Managing breast cancer in young women has become more complex thanks to the availability of a growing amount of data in this field. The management of these patients needs a dedicated approach involving a multidisciplinary team that takes into account their treatment and survivorship issues.²⁵

Prospective trials specifically focused to breast cancer in young women are needed to further improve the management of these patients.

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